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6. AUTHOR(S)
J. L. Matthews, Ph.D., Principal Investigator

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Baylor Research Institute, Dallas, TX
Biomedical Engineering Dept., Univ. Texas, Austin
UT-MD Anderson, Laser Biology Research Lab

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13. ABSTRACT *(Maximum 200 words)*

Baylor Research Institute, in collaboration with the Dept. of Biomedical Engineering at U.T. Austin and the Dept. of Laser Science at UT-M.D. Anderson hospital in Houston evaluated potential uses for high peak power pulsed and continuous wave lasers and the free-electron lasers at Duke, Stanford, and Vanderbilt for medical use. Resulting developments for potential medical use include eradication of viruses in blood banking, development of photoproducts for use in treatment of AIDS and cancer, photochemicals for non-thermal tissue welding, devices to augment thermal welding, systems for cartilage repair, combined wavelength lasers for tissue hemostasis and ablation, and a new family of photochemicals for use in tracking tumors and with potential as bonding agents in material science. Basic knowledge of laser-tissue interactions was developed.

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BAYLOR RESEARCH INSTITUTE

3812 Elm St.
P.O. Box 710699
Dallas, Texas 75226
(214) 820-2687
FAX (214) 820-4952

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Department of the Navy
Office of Naval Research
Federal BUilding Room 582
300 East 8th St.
Austin, TX 78701-3273

Dear Sirs:

Please find enclosed requisite copies of the Final Technical Report for the MFEL program, contract number N00014-91-J-4065 at Baylor Research Institute. Thank you for your assistance.

Sincerely

J. L. Matthews

J. L. Matthews, Ph.D.
Principal Investigator

Final Technical Report

Baylor Medical FEL Program

1. Composition of Research Group -

The Baylor Medical Center group in Dallas teamed with the Biomedical Laser Laboratories of the University of Texas at Austin led by A. J. Welch and the Laser Biology Research Laboratory led by Steve Jacques of the University of Texas M. D. Anderson Cancer Center of Houston comprised the main core of the "Baylor" MFEL team. The major thrust of this team was the evaluation of laser-tissue interactions and the development of photochemistry as potential means of using the FEL in medical applications. We sought the three opportunities to evaluate the FEL by: 1) attempting to acquire and operate a Mark 1 Madey model of the FEL; 2) in concert with Texas A&M University and Wendel Chen of the University of Texas at Arlington and Mike Berry of Rice University we sought to build and operate an FEL at Baylor; and 3) in concert with the Boeing Corporation who developed a high peak power FEL capable of delivering high cw power in the visible spectrum. We did not win support for any of these 3 lasers so our program was focused upon using the FEL laser at Vanderbilt and at Stanford-Duke when available. In the interim periods, various commercial lasers were used to develop background information and to initiate further studies of potential uses for lasers in medicine, including high peak power pulsed lasers and conventional continuous wave lasers.

2. Key Projects and Accomplishments Over Duration of Program -

A. Dual Use Laser Applications -

In collaboration with Mr. D. Hulst of Lasermatic, we evaluated the potential for combined laser therapy to achieve hemostasis via coagulation concurrent with tissue ablation. This was achieved by using a broadly focused Nd/YAG laser beam with a CO_2 laser beam focused within the limits of the Nd/YAG beam. Since the Nd/YAG beam penetrated tissue more deeply and wider than CO_2 ablation beam, coagulated tissue was always in front of and lateral to the CO_2 cutting beam. Successful surgical ablation of highly vascular tissue such as liver and spleen was accomplished and ultimately led to FDA approved and clinical utility of the combined laser device. These data also provided the basis for future dual beam applications of the FEL.

B. Blood Banking Applications -

Transmission of infectious agents is a potential risk of transfusion of whole blood or blood products. With the rapid increase in number of HIV patients cam increased recognition of the importance of transfusion related transmission of infectious diseases. HIV, HBV, EBV, CMV, HTLV, hepatitis A, B, C and D are all viruses transmitted by blood as are the bacteria of Lyme's disease (*Borrelia*) and parasitic blood borne infections such as malaria, Chaga's disease (*Trypanosoma cruzi*) and *Leishmania* species as experienced in Desert Storm. We evaluated several classes of photochemicals for their potential as anti infectious compounds. Key to developing a system for blood purification was the development of chemicals that had preferential binding to virus, bacteria, or

parasite with minimal binding or uptake by important normal blood components such as RBC, platelets, and WBC. Many photochemicals activated by appropriate wavelengths of laser sources react generating highly reactive oxygen species that cause damage to adjacent cell membrane structures. We demonstrated up to 6 $\log_{10}$ viral kill using various photochemicals such as porphyrins, merocyanines, carbocyanines, mixed ring porphyrins, sapphyrins, texaphyrins, puerpurins, psoralens, etc. and found these to be less damaging to RBC and to platelets, thus offering a potential for eradication of infectious agents in blood prior to using the blood products for transfusion. In order to optimize the kill of infectious agents and the sparing of blood cells, we synthesized two new classes of photochemicals. One of these class of new photochemicals were 1,8-naphthalimide, selected because they could act photochemically in the absence of oxygen. It was hypothesized that the damage to RBC and platelets was due to the individual exposure to reactive oxygen species generated by laser excitation. The naphthalimides were lipophylic, were concentrated in the cholesterol rich lipids of viral envelopes, and were not taken up by membranes of blood platelets, the most labile compound of the normal blood formed elements. The mechanism of viral and infectious organism inactivation was found to be cross-linking of intramembrane and transmembrane proteins. These membrane proteins change conformation upon docking with a cell to achieve infection and require conformation change for other functions. Cross-linking blocked protein change and resulted in blocking of CD_4 binding in case of HIV and SIV, blocked viral invasions and replication and blocked syncytial cell formation, i.e., all enveloped viruses tested (HIV, SIV, EBV, HBV, hepatitis ABCD, HTLV) were inactivated to concentration of 10 $\log_{10}$ virus without compromising the aggregation properties, ATP, or degranulation of platelets. Platelets were functional for standard storage times.

RBC were most readily treated with porphyrin compounds. Although the second class of synthesized chemicals (texaphyrins) offered no advantages over other photochemicals for blood banking use, they have subsequently been reacted with gadolinium and are presently being employed in clinical trial as tumor imaging agents. The developed photochemicals proved effective against all enveloped viruses, against *T. cruzi* and *Leishmania* organisms, malaria of all forms and *Borrelia.* Various cw and pulsed laser sources, diode arrays, and light sources were evaluated to optimize dye/light exposure protocols. Additional support for this work was from Quadralogic Technologies, Vancouver, BC and a grant from NHLRB of NIH.

C. Bone Marrow Purging -

Some photochemicals are preferentially incorporated and/or retained by tumor cells. In treating patients who have relapsed following initial therapy, very toxic levels of chemotherapeutics are employed requiring removal of bone marrow prior to vigorous chemotherapy with return of marrow following chemotherapy. We explored the utility of treating isolated marrow cells photochemically in an effort to remove any tumor cells from marrow prior to its return to patient. Key to success of this approach is the extent to which normal marrow stem cells are spared while tumor cells are killed. Prior to photochemical studies, chemotherapeutic agents used to purge marrow of tumor cells resulted in loss of up to 80% of viable marrow stem cells. After screening numerous photochemicals, we demonstrated retention of 80% viable stem cells with 100% tumor cell kill using merocyanine compounds. This approach is now used in some marrow units. A xenon lamp with IR filtering to avoid thermal damage were found to be adequate for the task.

D. Use of Pre-activation of Photochemicals to Achieve Tumor Kill -

Photodynamic therapy of cancer is a relatively new approach having received FDA approval for limited use this year. The approach capitalizes on the retention of dye by tumor cells following IV administration and an incubation period of a few hours post infusion. The tumor is then irradiated with an appropriate laser source of selected wavelength in visible spectrum which results in singlet oxygen generation and subsequent lipid peroxidation and mitochondrial damage of the tumor cells. Although very successful when the tumor is accessible to the laser source, this approach is limited by tumor access in deep tissues and requires precise knowledge of the location of the tumor, i.e., metastasized cells will not be treated. We explored the possibility that photoproducts might have antitumor properties. We were led to this study by observations that the antitumor efficacy of a large battery of photochemicals of various classes did not always correlate with the capacity of the photochemical to generate singlet oxygen. Merocyanine 540 for example, was highly effective as an antitumor agent in *in vitro* studies of several cell cultures of different tumor types, but was not found to be an efficient generator of singlet oxygen. Studies on physical properties of photochemicals were done at the University of Texas in Austin in the fast kinetics spectroscopy labs directed by Dr. Tony Harriman, a collaborator on these studies. Photoproducts isolated from individual photochemials following activation by laser light were stored at -80°C and tested hours, days and weeks later for antitumor activity (singlet oxygen is a short-lived transient species (of the order of 10 μs in H_2O) with a short diffusion path before extinction). We established varying antitumor activity with photoproducts isolated from different classes of photochemicals and significant

antitumor effects with photoproducts of merocyanine 540. Clinical use of isolated photoproducts would offer significant advantages over standard (singlet oxygen dependent) photodynamic therapy if the photoproducts were not highly toxic to normal tissues, i.e., tumors would not have to be isolated and directly exposed to laser irradiation of photoproducts achieved by prior *in vitro* radiation could be used. We named this approach "pre-activation PDT" and did an *in vitro* and *in vivo* toxicity study to ascertain whether sufficient efficacy/toxicity ratio could be realized. We also initiated attempts to isolate and ultimately characterize and synthesize the major active photoproducts so that the resultant "drug" would consist of compounds of known composition, tissue distribution, and toxicity, all necessary if photoproducts were to be quality controlled as per FDA good manufacturing guidelines.

The major photoproducts of MC540 were isolated and synthesized in collaboration with Professor Dr. B. Franck of Muenster Germany and with Dr. Gardner of Baylor University. Toxicity of these isolates was established in normal primary human cell cultures, in mice, rats, rabbits, and rhesus monkeys and found to be less than comparable chemotherapeutic agents that act principally on dividing cell populations.

A grant was obtained from Army Breast Cancer program to support the further *in vivo* evaluation of the efficacy of these photoproducts on solid tumors of breast cancer and prostate cancer tumors transplanted to nude mice. Successful eradication of transplanted tumors has been achieved with no observable short or long term toxic effects.

E. Effects of Photoproducts on Free Virus, Viral Infected Cells, and Provirus Forms -

Since direct PDT photochemical killing of free virus and viral infected cells was established in the blood sterilization studies, we also initiated study of the use of photoproducts as antiviral drugs. Although blood of viral infected patients could be purged of virus using an extracorporeal irradiation of patients' blood, this approach to therapy was not deemed appropriate as HIV infected patients for example, have a preponderance of infected cells and free virus resident in lymphatic and other tissues and blood circulating forms represent only a small percentage of the total viral load. Blood purging could only be a palliative means of temporarily reducing the circulating virus. However, intravenous delivery of antiviral photoproducts could at least hypothetically, circulate via blood, ECF, tissue lymph, and cerebrospinal fluid to gain access to widely dispersed infections agents. We thus investigated the *in vitro* effects of MC540 and naphthalimide photoproducts against HSV, CMV, HIV, SIV, and VSV virus. Naphthalimide photoproducts totally blocked syncytial cell formation (cell to cell infection) in SIV and HIV infected cells. However, naphthalimide photoproducts were not effective against cell-free enveloped virus at concentrations up to 100 μm. Photoproduct inactivation of both cell-free and cellularly associated enveloped virus by treatment with photoproducts of MC540 proved to be as efficacious as Direct PDT kill of all enveloped virus. Whole animal toxicity of both MC540 and naphthalimide photoproducts was low as found in previous tumor studies. Thus a potential new antiviral compound was isolated from photoproducts of laser irradiated photochemicals. To achieve adequate quantities of "drug" for use in animal studies, a 10 x 10 ft. room was equipped with 500 fluorescent lights and mirrors to achieve

preactivation. We demonstrated efficient preactivation with a candela pulsed peak power laser and sought access to the Boeing FEL as it was the only laser source available capable of delivering visible light at adequate cw power levels with sufficient beam diameter to permit large scale volume production of photoproducts essential for phase I clinical trial activity. We sought funding for this activity in collaboration with Boeing Corporation submitting an application to the "dual use" DOD program. We were not successful in this highly competitive arena. Our need for the FEL was supplanted by our successful chemical synthesis of the photoproducts of MC540 eliminating the need for laser irradiation. Isolation and synthesis of naphthalimide photoproducts has not been achieved due to lack of funding.

F. Use of Photochemicals and Dyes for Tissue Welding -

Cross-linking and fusion of connective tissue fibrils, bundles and sheaths using thermal laser sources such as the medical CO_2 laser has been used to achieve reanastamosis of blood vessels, nerves by fusing the tunica and ventitia of vessels and the epineurium of nerve. Binding of collagen-rich tissues such as fascia, ligaments, tendons, aponeuroses, etc. is readily achieved by delivering infrared energy to the zone of fusion which results in denaturation of protein, uncoiling and fraying of uncoiled ends, loss of order and axial periodicity, and resultant melding of apposed parts. Successful bonds have been achieved, possessing adequate bond strength evidenced by tests of bond tensile strength and resistance to shear and by the fluid bearing competency of welded blood vessels.

Direct thermal welding suffers from the drawback of damage to collateral tissues unless the beam can be narrowly focused and the thermal delivery pulsed to minimize thermal diffusion from weld sites to adjacent tissue. To enhance welding resolution and reduce collateral thermal diffusion, we developed a device to deliver dyes whose absorption maximum were coincident with delivered wavelengths of visible and IR laser light sources. This development was done in collaboration with MicroFab Technologies, Inc. of Plano, Texas. The piezo electric-driven tubular jets of the device (an ink jet printer system) were used to direct dye onto tissue substrates with orientation (both spatial and temporal) of the optical axis coinciding with the pulsed dye delivery system. This system was reduced to practice and several papers have been presented employing this system for tissue welding and for ablation and shaping of both dental tissues and ear ossicles.

G. Use of Photochemicals to Achieve Non-Thermal Tissue Bonding -

The ideal tissue bonding system would cause no collateral damage by denaturation of protein and would achieve bonds via co-valent chemical links such that maximum tensile strength and resistance to shear would be attained where the bond is equal to that of bulk intact tissue. Using oxygen independent 1,8-naphthalimide photochemical synthesized in our labs, we have achieved covalent links between certain amino acids of collagen (lysine, hydroxylysine, tryptophan, tyrosine, methionine) and the photochemical naphthalimide dyes. By creating dyes with two reactive ends separated by carbon chains of variable length, it is possible to span interfibril distances and to covalently link each end of the dye to a collagen fibril, achieving a tissue bond that is stable against protease and collagenase attack. Electrophoretic studies of bonded proteins and

ultrastructural studies and enzyme digest studies confirm stable bonding of collagen fibrils requiring no thermal energy but rather, occurring as a consequence of photochemical reactions upon irradiation with visible light. Dye size, charge, and lipophylicity has been modified to permit bonding or welding of two tissue surfaces together ordinarily resistant to bonding because of the presence of large quantities of anionically charged proteoglycans ensheathing collagen fibrils. Three such difficult tissues bonded by this system are cartilage, joint meniscus tissue, and cornea. Support for continued development of the cartilage and meniscus bonding system was won from the American Arthritis Foundation and work at this time has been extended to clinical trials in sheep joints using naphthalimide dyes and blue semiconductor laser light. The corneal work is the subject of an SBIR application to NASA made by SY Technologies, Inc., Huntsville, AL who are producing a unique optical delivery system capable of delivering a ring of blue laser light for corneal transplant welding applications. This work was initiated in the MFEL program and currently is being done in collaboration with Dr. George Timberlake of the Ophthalmology Department of the University of Kansas Medical Center, Kansas City, MO.

H. Pulsed FEL IR Pumping of 1,8-naphthalimides for Crosslinking with Nucleophiles in Prostheses and Tissues -

The photochemical cross-linking of proteins by the 3-halo-4-alkylamino-naphthalimides is a process requiring specific structural features in the protein. This is evidenced by the different light exposures at λ_{abs} = 425 nm required for viral inactivation, typically 20J/cm^2. These differences probably arise from different mechanisms involving rapid covalent reaction between the dye and electron-rich amino acid residues in viral proteins such as tryptophan as embodied in our proposed photoautomerization single electron transfer mechanism of the photoakylation and a tentatively proposed mechanism featuring less energetically favored Michael-addition-rearomatization involving hydroxylysine and lysine residues of collagen.

One of the most important factors in our choice of the naphthalimide nucleus is its chemical stability. Substitution of the amide nitrogen by another group under normal conditions is extremely difficult. The amide linkage of 1,8-naphthalimide differs from protein amide linkages in having two carbonyl stretching frequencies; e.g., asymmetric and symmetrical stretch frequencies near 1690 and 1650 cm^{-1}, respectively (measured in cyclohexane for the unbrominated analog of Ed66Br 1699 cm^{-1} (5.886 μM) and 1662 cm^{-1} (6.017 μM), respectively). The latter band, but not the former, is near the protein amide band near 1650 cm^{-1} (6.06 μM).

This difference will allow selective FEL IR excitation of the asymmetric stretch of the 1,8-naphthalimide carbonyl group in the presence of proteins, thus

potentially enhancing the reactivity of the amide group towards nucleophiles, especially of the amine-type present in collagen lysine and hydroxylysines.

We began a pilot experiment in collaboration with K.D. Straub, M.D., Ph.D. at the Duke MFEL facility in May 1993. We planned to study the potential IR-driven reaction between Ed66, the non-brominated analog of Ed66Br and aniline ($C_2H_5NH_3$). At this writing, the experiment still has not been performed. The IR photoirradiation cell was designed by us and was fabricated at Duke and the visible light optics train and photomultiplier installed for real-time sampling of the kinetics of formation of the reaction product. This was to have been done by following the blue absorption shift of circa -10 nm anticipated in the 415 nm absorption peak upon substitution of the aromatic ring of aniline for the akyl chain of the amide group. We still await IR beam availability at 5.886 μm wavelength following still ongoing replacement of FEL components at Duke.

Attainment of high asymmetrical stretch vibrational states should dramatically increase the polarity of the amide group. Both the increased polarity and vibrational amplitude should enhance the reaction coordinate motion for nucleophile (amine) addition to the carbonyl group in the initial reaction step leading to substitution of the amide nitrogen of the naphthalimide by the free amino nitrogen of the amino acid or protein residue. With a dimeric non-brominated 1,8-naphthalimide analog of DiEd66Br these reactions would lead to cross-linking of lysine and hydrosylysines of collagen. Thus, these reactions offer potential use of the rapid pattern flexibility MFEL in attachment of portions of collagen prostheses for transplant use during their manufacture. This flexibility in manufacture is not possible with existing technology.

I. Laser Ablation Mechanism Studies: Laser Biology Research Laboratory, M.D. Anderson (Jacques *et al*)

Our analysis has emphasized that tissue optics specify the primary zone of deposition of optical energy, called here the optical zone. The tissue absorption and scattering, the laser beam-width, and the size of pigmented structures can specify the optical zone. The laser-pulse duration can be sufficiently short that thermal diffusion is avoided and thermal energy is confined to the optical zone. The result is maximal laser-induced temperatures. The laser-pulse duration can also be sufficiently short that stress-wave propagation is avoided and stress induced by thermoelastic expansion to the optical zone is avoided. The result is maximal stress fields, which are able to propagate as stress waves to tissue sites outside the optical zone. The relationship between the optical zone and the pulse duration determines the laser-tissue interaction.

Limiting the thickness, hence volume, of the tissue optical zone in relatively non-absorbing tissues has been achieved by applying an absorbing pigment such as indoryanine green (IGG) to the surface. Our computer modeling study has disclosed four distinct phases which occur during tissue ablation upon lasing at 750-900 nm. The phases are: a) initial heating due to ICG absorption, b) evaporation with surface clamped at 100°C which desiccates surface layer, c) heating of surface after desiccation has slowed evaporation, d) rapid heating after onset of carbonization due to combination of desiccation and heating. Experiments with *ex vivo* human sclera specimens, ICG delivered with piezoelectrically driven (MicroFab, Inc.) droplets of 1% solution, and a 3-W

diode laser (2-mm dia. spot; 860 nm) demonstrated ablation and allowed comparison of theory and experiment.

The role of carbonization during laser ablation of tissue also was investigated. A dual-laser system was tested, in which a pulsed alexandrite laser thinned the carbon layer produced by a Nd:YAG laser. The thinning of the carbon layer modified the efficiency of ablation and the extent of surrounding thermal coagulation. Dual-laser irradiation offers a means of selecting between a cutting tool and a coagulation tool.

J. Tissue Optical Property Changes In Thermal Coagulation: Laser Biology Research Laboratory, M.D. Anderson (Jacques *et al*)

Studies have focused on relating, ultimately quantitatively, thermally-induced changes in tissue optical properties arising from laser irradiation energy input to the depths of thermal damage with a view to quantitatively monitoring damage during ablation and welding.

Thermal coagulation of albino rat skin heated *in vitro* was found to result in prominent changes of light scattering but relatively little in light absorption based on measurements using an integrating sphere spectrometer. The reduced scattering coefficients $\mu_s(1\text{-}g)$, gradually increase as temperatures increase from room temperature to 55°C then rapidly decrease to plateau after 70°C is reached. The differences among the $\mu_s(1\text{-}g)$ values for the different wavelengths were greater at the lower temperatures than at higher temperatures. The absorption coefficient, μ_a, changed very little over the test temperature range (room temperature to 90°C) and then only at higher temperatures and for longer wavelengths. The optical property changes were associated with thermally

induced light microscopic and ultrastructural changes in the dermal collagen, a major tissue component of skin.

Thermal fusion or welding of collagen-rich tissues involves the thermal denaturation of collagen which is reflected by changes in birefringence intensity in histologic sections. The weld bond between two severed edges is formed when the apposed ends of the collagen fibrils unravel during heating the re-entwine during the cooling phase. Thermal coagulation of collagen can be described as an end point of a kinetic rate process of thermal damage which is linear with time of exposure and exponential with temperature. The kinetic rate coefficients, A (s^{-1}) and E (J/mole) in the Arrhenius formulation, have been experimentally determined for birefringence loss in rat skin collagen heated *in vitro* — A = 1.606 X 10^{45} and E = 3.06 x 10^{5}. Loss in collagen birefringence is a rare quantitative indicator of thermal damage; in this case, the structural alteration in tissue native-form collagen. The kinetic model coefficients were derived from exposure times between 600 and 6000s over the temperature range 45 to 90°C. Room temperature control specimens were also analyzed for comparison.

K. Biomedical Laser Laboratories at the University of Texas at Austin, Feedback Control Mechanisms for Laser Assisted Surgery:

Since photothermally induced alteration of collagen substructure is believed to allow tissue fusion, temperature and tissue reflectance have been investigated as markers of thermal damage.

In a previous project, a robotic system that uses transient reflectance change to control the depth and the extent of laser induced retinal lesions in rabbit models was demonstrated. In another project, controlled temperature welding was implemented to control and limit the extent of thermal damage to tissue during laser assisted photothermal welding and to achieve higher weld strengths. A prototype automated system for constant temperature vessel welding was developed and quasi-constant temperature vessel welding was performed using *in vitro* human saphenous veins. Three to five millimeter long longitudinal incisions were sealed with irradiation from a shutter controlled argon ion laser (Trimedyne, Optilase™ Contact Laser System, Santa Ana, CA). A lead selenide detector (Infrared Industries, Orlando, FL) was employed to measure tissue surface temperature and the temperature signal from the detector controlled the laser radiation by closing the laser shutter whenever a preselected control temperature was exceeded. The average bursting pressure values (ranging between 90 and 120 mmHg) of controlled temperature welds at temperatures from 100 to 120°C were 80% higher than welds at temperatures from 70 to 90°C. The prototype system was also used to perform photothermal welding of canine jejunum *in vitro*. Eight to ten millimeter long longitudinal incisions on canine jejunum were sealed with irradiation from an argon ion laser (COHERENT, Innova 100-20, Palo Alto, CA) and the surface temperature on the site of impact was monitored without feedback control. The welded incisions did not leak within the intraluminal pressure was raised to 75 mmHg. It was observed that successful seals were created at irradiances of 140 to 280 mW/mm^2 which produced surface temperatures above 80°C.

Currently, a surgical device for temperature feedback-controlled laser surgery is under development. This device incorporates laser delivery and a temperature

feedback sensor into one single housing. The need to coalign/cofocus the temperature sensor and the laser beam before each experiment has been eliminated. This surgical device attached to the controlled temperature system has been used to compare controlled temperature tissue welding to uncontrolled laser tissue welding on *in vitro* and *in vivo* rat intestine.

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